ORAL CONTRACEPTIVES AND REDUCED RISK OF BENIGN BREAST DISEASES

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Abstract In 1970 a questionnaire on oral-contraceptive use was mailed to 97,254 married women 25 to 49 years of age in Greater Boston. Sixty-nine per cent responded. During the subsequent 30 months, 1072 of the women were hospitalized for breast diseases. Hospitalization rates for fibrocystic disease were similar for non-users of oral contraceptives and users of one to 12 months' duration. However, users for 13 months to 24 months and 25 or more months had rates only 70 and 35 per cent, respectively, of those of non-users. Detailed analysis of these results, and their similarity to findings in previous studies, suggest that the association is causal — use of oral contraceptives appears to lower risk of fibrocystic breast disease. A similar association was seen for fibroadenoma. Rates of breast cancer were lower for users than for non-users, but this finding was neither related to duration of use nor statistically significant. (N Engl J Med 294:419-422, 1976)

THERE have been several case-control studies on use of oral contraceptives and breast disease.[1-6] Women with breast cancer have shown no unusual frequency of use. However, previous results consistently suggest that oral contraceptives may protect against benign breast disease. The explanation of this apparent protection remains in doubt, in part because factors that affect a woman's contraceptive choice may relate to her risk of development of benign breast disease or use of medical services for such conditions. It therefore seemed appropriate to study the relation using a prospective cohort study. One such investigation supports the findings mentioned above but is based on few cases of benign breast disease.[7] We report here first results from a prospective cohort study begun in 1970. The analysis is based on 1072 cases of breast disease, benign and malignant, diagnosed through August, 1972.

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METHODS

The study group consisted of nearly all married women born between 1920 and 1944 who in 1969 lived in Boston or 14 contiguous towns to the south and west. The women were identified from Residents Lists compiled annually by every city and town in Massachusetts. In March, 1970, 97,254 women were mailed a request for information on number and ages of children, education, use of oral contraceptives and recent hospitalizations. Those who had used oral contraceptives were asked when they began, if they were still using them, when they had stopped and the total duration of use. After three mailings, 67,500 women (69.4 per cent) had provided information. The respondents were categorized as non-users, short-term users (cumulative duration of use less than 25 months) or long-term users (cumulative use 25 or more months).

Person-years of observation were computed for each woman. For respondents the observation period began on the date of the mailing responded to; for non-respondents it began on the date of the first mailing. For all women the observation period ended on August 31, 1972, or on the date a woman was first diagnosed as having breast disease. In the review of hospital records, described below, it was learned that 363 respondents and 122 non-respondents had had breast disease diagnosed before the study period; they were excluded from this analysis. In sum, the 69,137 eligible respondents and the 29,632 eligible non-respondents

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were observed for 149,678 and 71,281 person-years, respectively.

Women for whom histologically confirmed breast disease was first diagnosed from March, 1970, through August, 1972, were identified by surveillance of all but two of the 35 general or relevant specialty hospitals in the study area; the two that did not participate are small. Names of women identified from pathology log books or discharge lists were compared with the study roster to determine which were members of the study cohort.

Hospitalization rates were computed per 1000 person-years. To the extent that all patients with breast disease are hospitalized for diagnosis, our hospitalization rates reflect actual incidence rates. Some cases of benign breast disease occurring in our cohort are likely to have gone undetected because they were diagnosed in a physician's office. We do not know what fraction of the total this group represents. Where noted, the rates are age-standardized. Unless otherwise specified, the standard is the age distribution in five-year groups of all 97,254 women in the study. Age-standardized rate ratios and their 95 per cent confidence limits were computed as described by Miettinen.[8,9] The rate ratio expresses the hospitalization rate for the group of interest relative to a rate of unity for the non-users of oral contraceptives. When the upper confidence limit of a rate ratio is less than unity, the rate ratio is statistically significantly low, with $P<0.05$. Trends were tested for statistical significance by the method of Mantel.[10]

In March, 1973, a second questionnaire was sent to all 18,646 women who responded to the first questionnaire stating that they had used oral contraceptives and to an equal number of non-user respondents. Non-users were matched to the users for year of birth (decade), parity (0, 1-3, 4+), age at completion of education (<19, 19+ years), and town of residence. Of the 37,292 questionnaires mailed, 23,988 (64 per cent) were returned. The 1973 questionnaire is used in this analysis to evaluate possible selective out-migration, and to classify users of oral contraceptives for recency of use. Some women who were non-users as of 1970 indicated that they used oral contraceptives between 1970 and 1973. To maintain the prospective nature of the study, such women remain classified as non-users. Among the non-user respondents to the 1973 questionnaire, 6.1 per cent of the person-years of observation and 6.6 per cent of the cases of breast disease occurred in women who started using oral contraceptives after 1970. The percentages are small and similar — that is, women who began use after 1970 had a breast-disease hospitalization rate characteristic of the study group as a whole.

Results

The surveillance identified 1072 women with breast disease in the study cohort; 137 malignant and 659 benign cases were identified among respondents, and 39 malignant and 237 benign cases among non-respondents. Among respondents the cases of benign disease included 76 per cent with fibrocystic disease (or closely related diagnoses), 13 per cent with fibroadenoma and 11 per cent with other conditions, including women with both fibrocystic disease and fibroadenoma. The 11 per cent of women with "other" breast conditions were excluded from this analysis. Their use of oral contraceptives resembled that of the other women with benign disease, but they were too few for detailed analysis.

Table 1 shows hospitalization rates, according to age, for the three listed conditions among all 96,769 eligible women in the study cohort. Rates for fibrocystic disease rise with age from 0.7 in the youngest group to 4.8 among women 40 to 44 years of age and then decline slightly among women 45 to 49. Rates for fibroadenoma are fairly constant from 25 to 39 years of age at 0.7 per 1,000 person-years and then decline. As expected, breast-cancer rates rise steadily with age.

Table 1. Person-Years of Observation and Hospitalization Rates for Breast Diseases According to Age.

Age Group	Person-Yr	Rate/1000 Person-Yr		
		Fibrocystic disease	Fibroadenoma	Cancer
25-29	39,031	0.7	0.7	0.1
30-34	38,338	1.6	0.7	0.3
35-39	42,289	3.1	0.7	0.6
40-44	48,524	4.8	0.4	1.3
45-49	52,777	4.1	0.2	1.3
No. of women	—	679	112	176

Table 2 shows age-standardized hospitalization rates for the three diseases according to response status and use of oral contraceptives. For all conditions, the rates are about one third lower for non-respondents than for respondents. The Residents Lists from which the study members were identified were made up about 15 months before the questionnaires were mailed. Women migrating from the study area during the interval would probably be non-respondents and also have a lower probability of being identified if breast disease developed. The likely magnitude of out-migration and its effect on the findings are discussed later.

The clearest relation of hospitalization rates to use of oral contraceptives is seen for fibrocystic disease. Although short-term users appear to have rates little different from those of non-users, long-term users have, relative to non-users, an age-standardized rate ratio of 0.4 (95 per cent confidence limits, 0.3 to 0.6). Further simultaneous standardizations for age and either age at first birth, education or parity do not materially alter this finding. Furthermore, the substantial number of cases of fibrocystic disease among short-term users permits a finer classification according to duration of use. For users of one to 12 months' duration the standardized rate ratio was 0.9 whereas for users for 13 to 24 months, it was 0.7 (0.4 to 1.1). Thus, although use of oral contraceptives for less than 13 months is not associated with a reduction in the hospitalization rate for fibrocystic disease, continued use

Table 2. Hospitalization Rates* for Breast Diseases According to Response and Use of Oral Contraceptives.

Category	Rate/1000 Person-Yr		
	Fibrocystic disease	Fibroadenoma	Cancer
All respondents	3.4 (499)†	0.6 (83)	0.9 (137)
Non-users	3.7 (422)	0.6 (58)	1.0 (115)
Users for <25 mo	3.4 (56)	0.7 (18)	0.6 (12)
Users for ≥25 mo	1.3 (21)	0.3 (7)	0.7 (10)
Non-respondents	2.5 (180)	0.4 (29)	0.5 (39)

*Age-standardized. †Figures in parentheses represent numerators of the rates.

thereafter is associated with progressive decline in risk (based on chi-square for linear trend, $P = 10^{-6}$).

The association between use of oral contraceptives and fibrocystic disease can also be examined according to age (Table 3). The low rate among long-term users is seen in all age groups studied, and among younger women, low risk may be associated even with short-term use. With responses to the 1973 questionnaire, users were classified according to recency of use. Women who used oral contraceptives in 1970 or before and who used them between 1970 and 1973 were classified as "recent" users. Women who used them only in 1970 or before were classified as "non-recent" users. There are few non-recent long-term users (3800 person-years of follow-up observation), but with respect to fibrocystic disease their standardized rate ratio, 0.5 (0.2 to 0.9), is identical to that of recent long-term users, 0.5 (0.2 to 0.7). That is, the effect of oral contraceptives on risk of fibrocystic disease appears to persist for at least several years after cessation of use. Despite the small numbers this result is statistically significant.

Table 3. Hospitalization Rates for Fibrocystic Disease According to Duration of Use of Oral Contraceptives and Age.

Age Group	Rate/1000 Person-Yr		
	Non-user	Use for <25 mo	Use for ≥25 mo
25-29	1.3	0.6	0.5
	(15)*	(5)	(3)
30-34	2.3	1.4	1.6
	(37)	(8)	(8)
35-39	3.6	3.4	1.0
	(76)	(15)	(4)
40-44	5.5	5.4	1.1
	(144)	(18)	(3)
45-49	5.0	5.2	2.2
	(150)	(10)	(3)

*Figures in parentheses represent numerators of the rates.

For fibroadenoma the standardized rate ratio for short-term users is 1.2 (0.7 to 2.2), and that for long-term users 0.5 (0.2 to 1.2). For breast cancer, both short-term and long-term users have a standardized rate ratio of about 0.7 (0.5 to 1.4 and 0.5 to 1.6, respectively). In other words, for neither condition are the hospitalization rates for either group of users significantly lower than those for non-users. Numbers of admissions for fibroadenoma or cancer are insufficient for analyses according to age or recency of use.

This study also provides information on the relation of breast cancer and fibrocystic disease to reproductive history. One of the strongest risk indicators for breast cancer is the age at which a woman has her first child; the older she is at this event, the higher the risk of breast cancer.[11,12] This finding is confirmed by the data shown in Table 4, which is restricted to non-users of oral contraceptives. Women whose first child is delivered before the age of 23 have only half the breast-cancer rate of women whose first child is delivered after 26 (based on test for trend, $P = 0.03$). Unlike breast cancer, fibrocystic disease appears unrelated to the age at first birth. However, rates of

Table 4. Hospitalization Rates* for Fibrocystic Disease and Breast Cancer According to Age at First Delivery Among Non-users of Oral Contraceptives.

Age at 1st Delivery	Rate/1000 Person-Yr	
	Fibrocystic Disease	Cancer
<23	3.9	0.7
	(79)†	(15)
23-26	4.1	1.1
	(173)	(46)
≥27	3.9	1.4
	(133)	(50)
Nulliparous women	5.1	0.3
	(34)	(2)

*Standardized to age distribution of all non-users.

†Figures in parentheses represent numerators of the rates.

fibrocystic disease are strongly and inversely related to parity. Age-standardized hospitalization rates decline consistently with increasing parity from 5.1 per 1000 person-years for nulliparas to 2.4 for women of parity 5+ (based on chi-square for trend, $P = 7.7 \times 10^{-6}$). Both these findings for fibrocystic disease are similar to those of Kelsey et al.[4]

Discussion

The most striking finding in these data is the low hospitalization rate for fibrocystic breast disease among women who have used oral contraceptives for 25 months or longer. The finding is similar to those of most previous reports, although in two British studies the protective effect was largely restricted to *recent* long-term users.[1,7] Even in the one study in which little overall association was found, current long-term users had only about half the risk of "chronic cystic disease" experienced by non-users.[5] The question, then, is whether long-term use protects against fibrocystic breast disease or whether the association is non-causal and due to methodologic errors or selection bias.

This study lacks some of the difficulties of previous investigations, but has its own. Probably the most serious is that our ascertainment of the occurrence of disease in subjects depends both on the continued residence of subjects in the study area and on the stipulation that they be hospitalized for biopsy confirmation of their breast disease. We have some assurance that ascertainment of breast-cancer cases was substantially complete. On the basis of age-specific incidence rates of breast cancer for married women in Greater Boston, 1971-1972, breast cancer would have been expected to develop in 180 women in the study group; 176 cases were ascertained. Population rates are not available to enable such comparisons for the benign diseases.

The effect of possible *differential* migration from the study area according to use of oral contraceptives has been examined in two ways. First, we thought that 1973 questionnaires returned to us by the post office as "undeliverable" represented an upper estimate of out-migration. Accordingly, we calculated "undeliverable" rates to the 1973 questionnaire according to age and use of oral con-

traceptives at the time of the 1970 questionnaire. These rates varied from 10 per cent in the oldest group of women to 25 per cent in the youngest. Undeliverable rates among users were consistently higher by an average of 6 per cent. However, this small differential migration by use is unlikely to affect our results: because fibrocystic disease and breast cancer are strongly age dependent and because migration out of the study area was highest at the ages when incidence of disease is lowest, the combination of these factors appears to nullify the possible effect of the greater mobility of users of oral contraceptives. Because this problem is so important in a study of this nature, we examined the possible effect of differential migration in another way.

The rate ratio for fibrocystic disease among long-term users of oral contraceptives was estimated for each year of observation. If selective migration accounted for some or all of the apparent decreased risk ratio of fibrocystic disease in long-term users, it would be expected that the ratio would decrease with the passing of time. However, the standardized rate ratios for long-term users are 0.3, 0.4, 0.4 in 1970, 1971 and 1972 respectively.

Another possible explanation of low rates of fibrocystic disease among users of oral contraceptives is a selection bias — that is, women who are susceptible to fibrocystic disease may refrain from use — either on medical advice or for some other unknown reasons. This explanation seems unlikely since the protective association gains in strength with increasing duration of use. A selection bias would probably appear as a strong early effect that would gradually dissipate. In the absence of selection bias as well as differential migration (of any substantial magnitude) and the consistency of the present results with those of earlier studies, it is reasonable to conclude that long-term use of oral contraceptives is causally related to low risk of fibrocystic disease.

For cancer, a more cautious view is indicated. It could be inferred that oral contraceptives would protect against breast cancer, since they protect against fibrocystic disease and breast-cancer risk is increased among women who have undergone biopsy for benign breast diseases.[13] However, the few case-control studies so far reported suggest neither unusually high nor unusually low breast-cancer rates among women who use oral contraceptives. Moreover, because of the long latency period of breast cancer the relation of the disease to use of oral contraceptives will probably not be clarified for another decade or more. Two findings in the present study caution against the inference that use of oral contraceptives will lower breast-cancer risk. These are the absence of a dose-response relation in our data for breast cancer (though this may be due to chance) and the differences between breast cancer and fibrocystic disease in their relations to parity and age at first birth.

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